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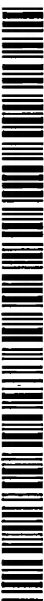


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**WO 02/072073 A2**

(54) Title: **ATORVASTATIN CALCIUM IN A PHARMACEUTICAL FORM, COMPOSITION THEREOF, AND PHARMACEUTICAL FORMULATION COMPRISING ATORVASTATIN CALCIUM**

(57) Abstract: Atorvastatin calcium, the substance known by the chemical name (R-(R\*,R\*))-(4-fluorophenyl)- $\beta$ , $\delta$ -dihydroxy-5-(1-methylethyl)-3-phenyl-((phenylamino)carbonyl)-1H-pyrrole-1-heptanoic acid hemi calcium salt is known as HMG-CoA reductase inhibitor and is used as an antihypercholesterolemic agent. Atorvastatin in the pharmaceutical compositions available in the market, is usually prepared as its calcium salt since it enables atorvastatin to be conveniently formulated in the pharmaceutical formulations, for example, in tablets, capsules, powders and the like for oral administration. Atorvastatin calcium can exist in an amorphous form or in one of the at least four known crystalline forms (Form I, Form II, Form III and Form IV). Atorvastatin calcium is the substance which is sparingly soluble in water, with pKa 4.5, and it has been found that the crystalline forms are less soluble than the amorphous form, which may cause problems in bioavailability of atorvastatin in the body. The present invention solves the problem of providing therapeutic equivalence of atorvastatin pharmaceutical formulation regardless the form (crystalline, amorphous, mixture of both) of atorvastatin calcium used for its preparation.

**Atorvastatin Calcium in a Pharmaceutical Form, Composition thereof,  
and Pharmaceutical Formulation comprising Atorvastatin Calcium**

The present invention relates to atorvastatin calcium in a  
5 novel pharmaceutical form, a novel composition comprising  
atorvastatin calcium, and a pharmaceutical formulation  
comprising said atorvastatin calcium or said composition of  
atorvastatin calcium. Furthermore, the present invention  
10 relates to a process for the preparation of said pharmaceutical  
formulation and the use of said pharmaceutical formulation  
comprising atorvastatin calcium as active ingredient for the  
treatment of hypercholesterolemia, hyperlipidemia and the like.

Atorvastatin calcium, the substance known by the chemical  
name (R-(R\*,R\*)) -2-(4-fluorophenyl)- $\beta$ , $\delta$ -dihydroxy-5-(1-methylethyl)-  
15 3-phenyl-((phenylamino)carbonyl)-1H-pyrrole-1-heptanoic acid hemi  
calcium salt is known as HMG-CoA reductase inhibitor and is  
used as an antihypercholesterolemic agent. Processes for the  
preparation of atorvastatin and key intermediates are disclosed  
in the United States Patent Numbers: 5,003,080; 5,097,045;  
20 5,103,024; 5,124,482; 5,149,837; 5,155,251; 5,216,174;  
5,245,047; 5,248,793; 5,280,126; 5,342,952 and 5,397,792.  
Atorvastatin in the pharmaceutical compositions available in  
the market, is usually prepared as its calcium salt since it  
enables atorvastatin to be conveniently formulated in the  
25 pharmaceutical formulations, for examples, in tablets,  
capsules, powders and the like for oral administration.

Atorvastatin calcium can exist in an amorphous form or in  
one of the at least four known crystalline forms (Form I, Form  
II, Form III and Form IV), which are disclosed in the patent  
30 applications WO 97/3958 and WO 97/3959. It is known that the  
amorphous forms of many pharmaceutical substances exhibit  
different dissolution characteristics and bioavailability  
patterns compared to the crystalline forms (Konno T., *Chem.  
Pharm. Bull.*, 1990;38;2003-2007). Bioavailability is one of the

key parameters for many therapeutic indications and is dependent on the form of the substance to be used in the pharmaceutical formulation. Processes for the crystallization and the preparation, respectively, of the amorphous substance  
5 are sometimes difficult to be performed, and as a product afford amorphous-crystalline mixtures with a changeable ratio of both forms, that is, crystalline form instead of amorphous form and vice versa. Since there are differences in the solubility among individual atorvastatin forms, as the patent  
10 application WO 97/3960 particularly emphasizes, also having an indirect impact on its bioavailability, it is very important to ensure uniformity of the substance being employed in a pharmaceutical formulation. Further, in the experiment it was observed that in acidic environment all atorvastatin calcium  
15 incorporated in a pharmaceutical formulation could not be dissolved because of the poor solubility of atorvastatin calcium and preparing a pharmaceutical formulation being constantly therapeutically equivalent was rendered impossible.

The problem of uniformity of atorvastatin calcium may be  
20 solved by employing the processes in its finalization which provide constant physical characteristics of the product. The problem occurs when atorvastatin calcium of mutually variable physical characteristics from several different sources is used for the preparation of a pharmaceutical formulation. Optionally  
25 the problem can be solved by preparing atorvastatin calcium as a crystalline form only (WO 97/3958 and WO 97/3959) and an amorphous form only (WO 97/3960, WO 01/42209, and Slovene patent application P-9900271), respectively, before it is incorporated in the formulation, which requires the use of an  
30 additional operation resulting in 5 to 10% loss. Since the patient should be provided with the drug being constantly therapeutically equivalent regardless to the form of atorvastatin calcium (regarding physical characteristics) incorporated in a pharmaceutical formulation, we have decided  
35 to solve the problem of the solubility of different forms of

atorvastatin calcium and consecutively its bioavailability at the level of the formulation. A further argument for this decision is the fact that atorvastatin calcium is an extremely expensive substance and all additional operations whereat a loss of the substance is possible considerably reduce the economical production process.

The patent literature describes atorvastatin calcium as an unstable substance and offers numerous solutions to provide a stable atorvastatin pharmaceutical formulation. Thus, for example, the stability of the formulation can be provided by the addition of a basic or a buffering agent to the formulation (WO 00/35425, WO 94/16603), namely by stabilizing the substance according to an analogous method described for pravastatin sodium in the patent application WO 01/93860. In order to prepare a stabilized amorphous substance, a combination of the methods disclosed in WO 01/93860, Slovene patent application P-9900271, and WO 01/42209 can be used. Insofar none of the described solutions on atorvastatin pharmaceutical compositions and formulations solves the problem of uniformity of atorvastatin calcium regarding the physical parameters (crystalline and amorphous form, respectively) and associated difficulties in providing therapeutic equivalence of atorvastatin calcium pharmaceutical formulation.

An object of the present invention is to solve the problem of providing therapeutic equivalence of atorvastatin calcium in a pharmaceutical form or comprised in a composition or a pharmaceutical formulation regardless the form (crystalline, amorphous, mixture of both) of atorvastatin calcium being used for the preparation thereof. The object of the present invention also relates to a pharmaceutical formulation containing an alkalisng or a buffering substance which improves the bioavailability of atorvastatin by increasing its solubility and dissolution rate in aqueous solutions.

These and further objects are accomplished by the present invention as defined in the claims.

In a first aspect of the present invention the object may be accomplished by atorvastatin calcium in a pharmaceutical  
5 form having a pH equal to or greater than the  $pK_a+1$  of atorvastatin calcium.

Moreover, in a second aspect of the present invention the object may also be accomplished by a composition comprising atorvastatin calcium providing a pH equal to or greater than  
10 the the  $pK_a+1$  of atorvastatin calcium to an aqueous solution thereof.

Furthermore, according to a third aspect of the present invention the above object may further be accomplished by a pharmaceutical formulation comprising atorvastatin calcium as  
15 active ingredient, wherein the pharmaceutical formulation when dissolved in a liquid aqueous medium increases the pH of said medium to a pH equal to or greater than the  $pK_a+1$  of atorvastatin calcium.

Further objects of the present invention can be achieved  
20 by preferred embodiments as set forth in the dependent claims.

The features of the present invention will become more apparent from the following description of the preferred embodiments.

The inventors surprisingly found that atorvastatin calcium  
25 in a pharmaceutical form according to the present invention or a composition comprising atorvastatin capable of providing a pH equal to or greater than the  $pK_a+1$  of atorvastatin calcium to an aqueous solution improves the solubility of atorvastatin calcium dissolved therein such that it is negligible whether  
30 the amorphous or the crystalline form is dissolved.

More specifically, in the experiments the applicant has found that the solubility of atorvastatin calcium in aqueous

solutions is markedly improved at pH values equal to or greater than  $pK_a+1$  whereas surprisingly differences between atorvastatin calcium in crystal or amorphous form appear to be negligible. The  $pK_a$  of atorvastatin's terminal carboxyl group is 4.5. Based on the above, it is preferred that when pH in the gastric microenvironment equal to or greater than  $pK_a+1$ , more preferably pH of 6, is provided resulting from the composition or the pharmaceutical formulation according to the present invention comprising atorvastatin calcium, differences in the solubility will no longer be noticeable between different forms of atorvastatin calcium with different physical characteristics. The atorvastatin calcium forms having different physical characteristics which may be present in the composition or the pharmaceutical formulation according to the present invention can either be the amorphous form, the crystalline form or both forms simultaneously. Moreover, the present invention is not limited to these forms, but any physical form of atorvastatin calcium can be present in the composition or the pharmaceutical formulation of the present invention. More preferably, the amorphous atorvastatin calcium may be present in a form having a large specific surface, in particular as micronized amorphous atorvastatin calcium. Atorvastatin having a large specific surface has a further improved solubility characteristic.

In order to adjust the pH of the aqueous solution in the appropriate range, the composition or the pharmaceutical formulation according to the present invention optionally comprises a pH adjusting substance. The adjusting substance suitably used in the present invention is not specifically limited, however a substance selected from the group consisting of metal oxides, inorganic bases, organic bases, and salts of organic and inorganic acids is preferable. More preferably used pH adjusting substances are selected of the group consisting of oxides or hydroxides of alkaline or alkaline earth metals, in particular  $MgO$ , alkaline phosphate buffers, in particular

$\text{Na}_3\text{PO}_4$  and  $\text{Na}_2\text{HPO}_4$ , and organic amines, in particular tris(hydroxymethyl)methylamine.

In the present invention, the pharmaceutical formulation when used for a single administration and comprising  
5 atorvastatin calcium as active ingredient preferably comprises the pH adjusting substance in an amount of 0.2 to 2.0 mmol, and more preferably of 0.4 to 1.2 mmol. If the pH adjusting substance is comprised in the above specific range, the pH  
10 value of 900 ml aqueous HCl solution, more generally the pH value of an simulated gastric environment of the stomach, may be properly adjusted by single administration of the pharmaceutical formulation according to the present invention. Thus, an improved solubility characteristic of the atorvastatin calcium contained in the pharmaceutical formulation can be  
15 achieved, irrespective whether the atorvastatin calcium is contained in the amorphous and/or crystalline form.

### Experiments

For *in vitro* simulation of preferred embodiments of atorvastatin calcium pharmaceutical formulations in acidic  
20 gastric environment of the stomach according to the present invention, the dissolution testing in a simulated gastric fluid having a pH value of about pH 3, and more specifically in 900 ml of aqueous 0.001M HCl solution, was performed. The concentration of dissolved atorvastatin was then measured at  
25 10-minute intervals.

Four different formulations were prepared in form of tablets (A1, A2, A3 and A4; their composition is shown in Table 1), which were capable of providing different pH of the aqueous solution (obtained pH values of the solutions are shown in  
30 Table 2). Measurement results of the amount of dissolved atorvastatin in % are shown in Table 3.

Table 1

Composition	A1	A2	A3	A4
Atorvastatin amorphous, micronized*	20.00	20.00	20.00	20.00
Microcrystalline cellulose (Avicel PH112 or PH102)*	98.60	78.60	72.60	37.10
Lactose monohydrate (70-100 mesh)	34.80	34.80	34.80	20.00
Cross-linked carboxymethylcellulose (Ac-di-sol)	9.60	9.60	9.60	9.60
Polysorbate 80	1.30	1.30	1.30	1.30
Hydroxypropyl cellulose (Klucel EF)	2.00	2.00	2.00	2.00
MgO	-	20.00	26.00	-
Na <sub>2</sub> HPO <sub>4</sub>	-	-	-	140.00
Microcrystalline cellulose (Avicel PH112)	71.90	71.90	71.90	48.20
Cross-linked carboxymethylcellulose (Ac-di-sol)	9.60	9.60	9.60	19.60
Aerosil 200	1.20	1.20	1.20	1.20
Mg stearate	1.00	1.00	1.00	1.00
TOTAL	250.00	250.00	250.00	300.00
Demi water for granulation	100.00	70.00	70.00	-
Ethanol refined (96%)	-	-	-	50.00

\*- Atorvastatin in the form of calcium salt in an equivalent amount, the difference is adjusted with an amount of microcrystalline cellulose

- 5 All quantities required for the preparation of one tablet are given in milligrams.

Table 2

	A1	A2	A3	A4
pH (1 tablet in 900 ml aqueous 0.001M HCl solution) after 15 min	3.22	4.28	6.09	6.06
pH (1 tablet in 900 ml aqueous 0.001M HCl solution) after 30 min	3.21	4.67	8.88	6.02

Table 3

	A1	A2	A3	A4
10 min	56.5	69.7	74.9	62.2
20 min	66.1	80.1	91.1	99.0
30 min	70.6	85.8	96.3	97.9
40 min	74.4	87.0	98.2	98.3
60 min	75.6	89.6	99.8	98.8

- 10 As evident from the measurements, all atorvastatin was dissolved advantageously in the case if the tablet was capable to increase the pH to a value that meets atorvastatin calcium's pKa+1, more specifically the pH of 900 ml of an aqueous 0.001M



HCl solution for three pH units, that is at least to pH 6. In these cases atorvastatin was dissolved at much faster rates.

In addition to improvement of the solubility, pKa+1 surprisingly also leveled the difference in solubility between atorvastatin calcium in a crystalline form and an amorphous form. To prove the above statement the granulations with the additions of different alkalising or buffering agents and different physical forms of atorvastatin calcium were prepared. Comparison of the release rate of atorvastatin from the granulations with added alkalising or buffering agents to the release rate of atorvastatin from the reference granulations with no added alkalising or buffering substances was carried out (Table 4). The pH values of solutions provided by different granulations are shown in Table 5. Measurement results of the amount of dissolved atorvastatin in % at different time intervals are shown in Table 6.

Table 4

Composition	AK1	AK2	AK3	AA1	AA2	AA3
Atorvastatin crystalline*	20.0	20.0	20.0	-	-	-
Atorvastatin amorphous*	-	-	-	20.0	20.0	20.0
Microcrystalline cellulose (PH102)*	71.3	71.3	71.3	71.3	71.3	71.3
Lactose monohydrate (70-100 mesh)	34.8	34.8	34.8	34.8	34.8	34.8
Cross-linked carboxymethylcellulose (Ac-di-sol)	9.6	9.6	9.6	9.6	9.6	9.6
Polysorbate 80	2.6	2.6	2.6	2.6	2.6	2.6
Hydroxypropyl cellulose (Klucel EF)	2.0	2.0	2.0	2.0	2.0	2.0
Tris	110.0	-	-	110.0	-	-
Na <sub>3</sub> PO <sub>4</sub>	-	80.0	-	-	80.0	-
Microcrystalline cellulose (Avicel PH112)	67.9	67.9	67.9	67.9	67.9	67.9
Cross-linked carboxymethylcellulose (Ac-di-sol)	9.6	9.6	9.6	9.6	9.6	9.6
Aerosil 200	1.2	1.2	1.2	1.2	1.2	1.2
Mg stearate	1.0	1.0	1.0	1.0	1.0	1.0
Demi water for granulation	80.0	80.0	80.0	80.0	80.0	80.0

\*- Atorvastatin in the form of Ca salt in an equivalent amount, the difference is adjusted with an amount microcrystalline cellulose

All quantities required for filling one capsule are given in milligrams.

Table 5

	AK1	AK2	AK3	AA1	AA2	AA3
pH (1 capsule in 900 ml aqueous 0.001M HCl solution) after 15 min	6.68	6.28	3.14	5.81	6.28	3.20
pH (1 capsule in 900 ml aqueous 0.001M HCl solution) after 30 min	6.95	6.72	3.15	5.68	6.30	3.24

Table 6

	AK1	AK2	AK3	AA1	AA2	AA3
10 min	64.6	49.9	31.8	75.9	50.8	38.7
20 min	76.4	63.4	44.5	82.6	62.1	53.4
30 min	81.0	72.3	51.4	83.6	68.5	61.5
40 min	84.2	77.3	55.8	83.9	72.8	66.6

From the obtained results it is evident that the percentage difference in the amount of dissolved amorphous and crystalline atorvastatin calcium was approximately 20% when the granulation without added alkalisng or buffering substance was used, and a difference appeared minimal (< 5%) when a buffering substance was added.

It was tried to additionally improve the solubility of amorphous atorvastatin calcium by enlarging the specific surface area of particles of the amorphous substance. Six different granulations were prepared in the same manner as in the previous experiment, the only difference being instead of crystalline atorvastatin, micronized amorphous atorvastatin calcium (AAM1, AAM2 and AAM3 samples) was used having several times larger specific surface area of the particles compared to nonmicronized. The pH values provided by the granulations are shown in Table 7. Measurement results of the amount of dissolved atorvastatin in % at different time intervals are shown in Table 8.

Table 7

	AAM1	AAM2	AAM3	AA1	AA2	AA3
pH (1 tablet in 900 ml aqueous 0.001M HCl solution) after 15 min	6.80	6.40	3.12	5.81	6.28	3.20
pH (1 tablet in 900 ml aqueous 0.001M HCl solution) after 30 min	6.76	6.44	3.30	5.68	6.30	3.24

Table 8

	AAM1	AAM2	AAM3	AA1	AA2	AA3
10 min	85.9	93.9	41.5	75.9	50.8	38.7
20 min	95.8	94.2	55.9	82.6	62.1	53.4
30 min	98.4	93.9	63.8	83.6	68.5	61.5
40 min	99.3	94.0	68.9	83.9	72.8	66.6

From the obtained results it is evident that there was practically no difference in the amount of dissolved amorphous and amorphous micronized atorvastatin when the granulation without added buffering agent was used, and the difference increased to more than 15 - 20 % when a buffering agent was added.

The aforementioned experiments surprisingly showed that it was possible to provide therapeutic equivalence of atorvastatin calcium in a pharmaceutical form, a composition thereof as well as pharmaceutical formulations regardless which form (crystalline, amorphous, mixture of both) of atorvastatin calcium was used for their preparation. Of paramount importance for providing the therapeutic equivalence is the capability of the atorvastatin calcium, the composition thereof, and the pharmaceutical formulation according to the present invention to provide a pH equal to or greater than the  $pK_a+1$  of atorvastatin calcium to an aqueous solution. In a preferred embodiment atorvastatin calcium, the compositions and the formulation of the present invention have the capability to increase the pH of 900 ml aqueous 0.001M HCl solution to pH values equal to or greater than  $pK_a+1$  or more, in particular pH 6 or more.

The other surprising finding was that the dissolved amount of micronized amorphous atorvastatin calcium in the granulation with added alkalising or buffering substance is approximately for 15% greater than in case of nonmicronized atorvastatin calcium. Here the most surprising fact is that an increase of a specific surface of the particles itself does not have an impact on the improvement of the solubility, as the solubility

of micronized and nonmicronized amorphous atorvastatin calcium in the granulation with no added alkalising or buffering substance is equivalent.

The pharmaceutical formulation, which is the object of the present invention, may contain, in addition to atorvastatin calcium, one or more fillers such as microcrystalline cellulose, lactose, sugars, starches, modified starch, mannitol, sorbitol and other polyols, dextrin, dextran and maltodextran, calcium carbonate, calcium phosphate and/or hydrogen phosphate, sulfate, one or more binders such as lactose, starches, modified starch, dextrin, dextran and maltodextrin, microcrystalline cellulose, sugars, polyethylene glycols, hydroxypropyl methylcellulose, ethylcellulose, hydroxyethyl cellulose, methylcellulose, carboxy methylcellulose, sodium carboxy methylcellulose, gelatin, acacia gum, tragacanth, polyvinylpyrrolidone, magnesium aluminum silicate, one or more disintegrating agents such as cross-linked sodium carboxy methylcellulose, cross-linked polyvinylpyrrolidone, cross-linked carboxymethyl starch, starches and microcrystalline cellulose, magnesium aluminum silicate, polyacrylin potassium, one or more different glidants such as magnesium, calcium and zinc stearate, calcium behenate, sodium stearyl fumarate, talc, magnesium trisilicate, stearic acid, palmitic acid, carnauba wax, silicon dioxide, one or more buffering substances such as sodium citrate, dibasic sodium phosphate, calcium carbonate, hydrogen phosphate, phosphate, sulfate, magnesium carbonate, potassium citrate, potassium sorbate, sodium ascorbate, benzoate, hydrogen carbonate, hydrogen phosphate, or one or more basic substances such as MgO, MgOH, NaOH, Ca(OH)<sub>2</sub>, tromethamine, Al Mg silicate, lauryl sulfate. If required, the formulation may also include surfactants and other conventional ingredients for solid pharmaceutical formulations such as coloring agents, lakes, flavoring agents and adsorbents. As surfactants the following may be used: ionic surfactants such as sodium lauryl sulfate or

non-ionic surfactants such as different poloxamers (polyoxyethylene and polyoxypropylene copolymers), natural or synthesized lecithins, esters of sorbitan and fatty acids (such as Span<sup>®</sup> (Atlas Chemie)), esters of polyoxyethylenesorbitan and fatty acids (such as Tween<sup>®</sup> (Atlas Chemie)), polyoxyethylated hydrogenated castor oil (such as Cremophor<sup>®</sup> (BASF)), polyoxyethylene stearates (such as Myrj<sup>®</sup> (Atlas Chemie)) or cationic surfactants such as cetyl pyridine chloride or any combination of the herein abovementioned surfactants.

The pharmaceutical formulations of the present invention may be provided either as solid pharmaceutical formulations, such as powders, granules, tablets, or capsules, for example, or as liquid pharmaceutical formulations, preferably filled in capsules.

The solid pharmaceutical formulations according to the present invention, may be prepared as described below:

- The mixture of the active ingredient, a filler, a binder, an alkalisng or buffering substance, a disintegrating agent and if required a surfactant and other conventional ingredients for solid pharmaceutical formulations is homogenized employing suitable mixers, the mixture is compacted using suitable compaction machines or slugged on slugging machines, the compacts or slugs are triturated and/or sieved, fillers, disintegrating agents, buffering substances, glidants, lubricants and other conventional inactive ingredients for tablets or capsules are added, and re-homogenized. The resulting mixture is compressed into tablets or filled into capsules.
- The mixture of the active ingredient, a filler, a binder, an alkalisng or buffering substance, a disintegrating agent and if required a surfactant and other conventional

ingredients for solid pharmaceutical formulations are homogenized employing suitable mixers, glidants and lubricants are added and re-homogenized. The resulting mixture is compressed into tablets or filled into capsules.

- 5 • The mixture of the active ingredient, a filler, a binder, an alkalising or buffering substance, a disintegrating agent and if required a surfactant and other conventional ingredients for solid pharmaceutical formulations are homogenized employing suitable mixers, granulated with a
- 10 suitable solvent such as water, ethanol, methanol, isopropyl alcohol, n-butyl alcohol, acetone, diethylether, ethylacetate, isopropyl acetate, methyl acetate, dichloromethane, chloroform, mixtures of these solvents such as ethanol and acetone, methanol and acetone,
- 15 dichloromethane and methanol, and the mixtures thereof. The resulting granulation is dried in suitable dryers such as standard tray dryers, fluidized bed dryers, vacuum and microwave dryers, at a temperature not exceeding 60°C. To the dried granulation, glidants, disintegrating agents,
- 20 alkalising or buffering substances, glidants and lubricants are added and if required other conventional ingredients for solid pharmaceutical formulations. The resulting mixture is re-homogenized and compressed into tablets or filled into capsules.

25        Optionally, tablets are film-coated.

The present invention is illustrated but in no way limited by the following examples.

**EXAMPLES****Examples 1-2**

Tablets with added MgO or Na<sub>2</sub>HPO<sub>4</sub>

The ingredients, listed in the table below, were  
 5 homogenized in a mixer and granulated with water and ethanol,  
 respectively. The resulting granulation was dried in a vacuum  
 dryer at a temperature not exceeding 60°C.

Composition	A3	A4
Atorvastatin amorphous, micronized*	20.00	20.00
Microcrystalline cellulose (Avicel PH112 or PH102)*	72.60	37.10
Lactose monohydrate (70-100 mesh)	34.80	20.00
Cross-linked carboxymethylcellulose (Ac-di-sol)	9.60	9.60
Polysorbate 80	1.30	1.30
Hydroxypropyl cellulose (Klucel EF)	2.00	2.00
MgO	26.00	-
Na <sub>2</sub> HPO <sub>4</sub>	-	140.00
Demi water for granulation	70.00	-
Ethanol refined for granulation (96%)	-	50.00

\*- Atorvastatin in the form of Ca salt in an equivalent amount,  
 the difference is adjusted with an amount of microcrystalline  
 10 cellulose

All quantities are given in milligrams (for one tablet). The  
 quantity of the prepared granulation was sufficient for the  
 preparation of 1000 units of 250 mg tablets.

To the dried granulation the following was added:

Microcrystalline cellulose (Avicel PH112)	71.90	48.20
Cross-linked carboxymethylcellulose (Ac-di-sol)	9.60	19.60
Aerosil 200	1.20	1.20
Mg stearate	1.00	1.00

15 The resulting mixture was re-homogenized and compressed  
 into tablets. The pH values provided by one tablet in 900 ml of  
 aqueous 0.001M HCl solution were the following:

	A3	A4
pH (1 tablet in 900 ml aqueous 0.001M HCl solution) after 15 min	6.09	6.06
pH (1 tablet in 900 ml aqueous 0.001M HCl solution) after 30 min	8.88	6.02

Examples 3-6

Capsules with amorphous and crystalline, respectively, atorvastatin calcium with added Tris and  $\text{Na}_3\text{PO}_4$ , respectively

- 5 The ingredients, listed in the table below, were homogenized in a mixer and granulated with water and ethanol, respectively. The resulting granulation was dried in a vacuum dryer at a temperature not exceeding 60°C.

Composition	AK1	AK2	AA1	AA2
Atorvastatin crystalline*	20.0	20.0	-	-
Atorvastatin amorphous*	-	-	20.0	20.0
Microcrystalline cellulose (PH102)*	71.3	71.3	71.3	71.3
Lactose monohydrate (70-100 mesh)	34.8	34.8	34.8	34.8
Cross-linked carboxymethylcellulose (Ac-di-sol)	9.6	9.6	9.6	9.6
Polysorbate 80	2.6	2.6	2.6	2.6
Hydroxypropyl cellulose (Klucel EF)	2.0	2.0	2.0	2.0
Tris	110.0	-	110.0	-
$\text{Na}_3\text{PO}_4$	-	80.0	-	80.0
Demi water for granulation	80.0	80.0	80.0	80.0

- 10 All quantities required for preparation of the granulation for one capsules are given in milligrams. The quantity of the prepared granulation was sufficient for filling 1000 capsules.

To the dried granulation the following was added:

Microcrystalline cellulose (Avicel PH112)	67.9	67.9	67.9	67.9
Cross-linked carboxymethylcellulose (Ac-di-sol)	9.6	9.6	9.6	9.6
Aerosil 200	1.2	1.2	1.2	1.2
Mg stearate	1.0	1.0	1.0	1.0

- 15 The resulting mixture was re-homogenized and compressed into tablets. The pH values provided by one tablet in 900 ml of aqueous 0.001M HCl solution were the following:



	AK1	AK2	AA1	AA2
pH (1 tablet in 900 ml aqueous 0.001M HCl solution) after 15 min	6.68	6.28	5.81	6.28
pH (1 tablet in 900 ml aqueous 0.001M HCl solution) after 30 min	6.95	6.72	5.68	6.30

Optionally, used atorvastatin could be micronized or prepared according to some other method to enlarge a specific surface area of the particles (e.g., grinding)

**Claims:**

1. Atorvastatin calcium in a pharmaceutical form of an aqueous solution having a pH equal to or greater than the  $pK_a+1$  of atorvastatin calcium.
- 5 2. A composition comprising atorvastatin calcium providing a pH equal to or greater than the  $pK_a+1$  of atorvastatin calcium to an aqueous solution thereof.
3. The composition according to claim 2 comprising further a pH adjusting substance.
- 10 4. The composition according to claim 3 wherein the pH adjusting substance increases the pH of an aqueous solution equal to or greater than the  $pK_a+1$  of atorvastatin calcium.
5. The composition according to any of the claims 2 to 4 wherein the pH is adjusted to 6 or more.
- 15 6. The composition according to any of the claims 2 to 5, wherein the pH adjusting substance is at least one substance selected from alkalising and buffering substances.
7. A pharmaceutical formulation comprising atorvastatin calcium as active ingredient,
- 20 **characterized in that**  
the pharmaceutical formulation when dissolved in a liquid aqueous medium increases the pH of said medium to a pH equal to or greater than  $pK_a+1$  of atorvastatin calcium.
8. The pharmaceutical formulation according to claim 7,
- 25 wherein the atorvastatin calcium is present in the formulation in different physical forms.

9. The pharmaceutical formulation according to claim 7 or 8, wherein the atorvastatin calcium is present in the formulation in a crystalline and/or amorphous form at the same time.

5 10. The pharmaceutical formulation according to any of the claims 7 to 9, wherein the atorvastatin calcium comprises amorphous atorvastatin calcium having a large specific surface of the particles.

10 11. The pharmaceutical formulation according to claim 10, wherein the atorvastatin calcium comprises micronized amorphous atorvastatin calcium.

12. The pharmaceutical formulation according to any of the claims 7 to 9, wherein the atorvastatin calcium comprises crystalline atorvastatin calcium.

15 13. The pharmaceutical formulation according to any of the claims 7 to 12, wherein the formulation provides in the simulated gastric fluid of pH of 3 a pH of equal to or greater than  $pK_a+1$ .

14. The pharmaceutical formulation according to claim 13, wherein the formulation provides a pH of 6.

20 15. The pharmaceutical formulation according to any of the claims 7 to 14, wherein the amount of the pH adjusting substance is adjusted in the formulation such that a single administration increases the pH of 900 ml aqueous HCl solution having a pH of about 3, in particular 900 ml of a 0.001 M HCl  
25 solution, to a pH equal to or greater than  $pK_a+1$  or more.

16. The pharmaceutical formulation according to any of the preceding claims, wherein the pH adjusting substance is contained in the pharmaceutical formulation in an amount of 0.2 to 2.0 mmol, in particular in an amount of 0.4 to 1.2 mmol.

17. The pharmaceutical formulation according to any of the claims 7 to 16, wherein the pH adjusting substance is selected from the group of metal oxides, inorganic bases, organic bases, and salts of organic and inorganic acids.

5 18. The pharmaceutical formulation according to any of the claims 7 to 17, wherein the pH adjusting substance is selected from the group consisting of metal oxides, oxides or hydroxides of the alkaline or alkaline earth metals, in particular MgO, alkaline phosphate buffers, in particular Na<sub>3</sub>PO<sub>4</sub> and Na<sub>2</sub>HPO<sub>4</sub>, and  
10 organic amines, in particular tris(hydroxymethyl)methylamine.

19. The pharmaceutical formulation according to any of the claims 7 to 18 in the form of a powder, granules, a tablet or a capsule.

20. The pharmaceutical formulation according to any of the  
15 claims 7 to 19 comprising further one or more components selected from the group of fillers, binders, buffering substances, basic substances, surfactants and other pharmaceutically acceptable ingredients.

21. A process for the preparation of a pharmaceutical formulation  
20 comprising atorvastatin calcium as active ingredient,

**characterized by the following steps:**

(a) mixing the active ingredient with at least one component selected from the group consisting of alkalising and/or buffering substances, fillers, binders, disintegrants, and  
25 surfactants;

(b) homogenizing the above mixture;

(c) adding additional ingredients to the above mixture;

(d) re-homogenizing the resulting mixture; and

(e) final processing the re-homogenized mixture in  
30 administrable form.

22. The process according to claim 21 wherein the final processing step (e) is compressing the re-homogenized mixture into tablets.

23. The process according to claim 21 wherein the final  
5 processing step (e) is filling the re-homogenized mixture into capsules.

24. The process according to any of the claims 21 to 23, further comprising the steps of:

- (f) compacting the mixture after homogenization; and
- 10 (g) further processing including triturating and/or sieving the compacted mixture before adding additional ingredients.

25. The process according to any of the claims 21 to 24, further comprising the steps of:

- 15 (h) granulating the homogenisate obtained in step (b) with granulation liquid; and
- (i) drying the obtained granulate before adding additional ingredients.

26. The process according to claim 24 or 25, wherein the additional ingredients are selected from the group consisting  
20 of fillers, binders, disintegrants, alkalising agents, and glidants.

27. The process according to any of the claims 21 to 26, wherein the addition of the pH adjusting substance is adjusted such that a single administration of the formulation increases  
25 the pH of the acidic environment to a pH equal to or greater than  $pK_a+1$  of atorvastatin calcium.

28. The process according to claim 27, wherein the addition of the pH adjusting substance is adjusted such that a single administration of the formulation increases the pH of the acidic environment to a pH of 5.5 or more.

5 29. The process according to any of the claims 21 to 28 for the preparation of a solid formulation according to any of the claims 7 to 20.

30. The use of a solid formulation according to any of the claims 7 to 20 or of a solid formulation prepared according to  
10 any of the claims 21 to 29 for the treatment of hypercholesterolemia and hyperlipidemia.

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19 September 2002 (19.09.2002)

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- (71) Applicant (*for all designated States except US*): LEK PHARMACEUTICAL AND CHEMICAL COMPANY D.D. [SI/SI]; Legal Affairs and Industrial Property, Verovskova 57, 1526 Ljubljana (SI).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): KERC, Janez [SI/SI]; Trebinjska 7, 1000 Ljubljana (SI). MATEJA, Salobir [SI/SI]; ul. 28. Maja 9, 1000 Ljubljana (SI). BAVEC, Sasa [SI/SI]; Mekinceva 15, 1000 Ljubljana (SI).
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- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*

(54) Title: PHARMACEUTICAL FORMULATION COMPRISING ATORVASTATIN CALCIUM

(57) Abstract: Atorvastatin calcium can exist in an amorphous form or in one of the at least four known crystalline forms (Form I, Form II, Form III and Form IV). Atorvastatin calcium is the substance which is sparingly soluble in water, with pKa 4,5, and it has been found that the crystalline forms are less soluble than the amorphous form, which may cause problems in bioavailability of atorvastatin in the body. The present invention solves the problem of providing therapeutic equivalence of atorvastatin pharmaceutical formulation regardless the form (crystalline, amorphous, mixture of both) of atorvastatin calcium used for its preparation.



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# INTERNATIONAL SEARCH REPORT

International Application No

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<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 7 A61K9/16 A61K9/20 A61K31/40 A61P3/06		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the International search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94 16693 A (WARNER LAMBERT CO) 4 August 1994 (1994-08-04) cited in the application page 4, line 30 -page 5, line 29 examples claims 1,2,8 ---	2-30
X	WO 00 35425 A (LEK TOVARNA FARMACEVTSKIH) 22 June 2000 (2000-06-22) cited in the application page 3, line 10 -page 4, line 20 example 6 ---	2-30
Y	WO 97 03958 A (WARNER LAMBERT CO) 6 February 1997 (1997-02-06) cited in the application page 13, line 27 - line 36 example 3 ---	1
-/-		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "Z" document member of the same patent family		
Date of the actual completion of the international search 13 November 2002		Date of mailing of the international search report 21/11/2002
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 851 epo nl, Fax: (+31-70) 340-3016		Authorized officer Epskamp, S



## INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	KEARNEY AS ET AL: "The interconversion kinetics, equilibrium, and solubilities of the lactone and hydroxyacid forms of the HMG-CoA reductase inhibitor, CI-981." PHARMACEUTICAL RESEARCH (NEW YORK), vol. 10, no. 10, 1993, pages 1461-1465, XP008010404 ISSN: 0724-8741 abstract figure 2 ---	1
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Form PCT/ISA/210 (patent family annex) (July 1992)

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/IB 02/00736

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claim 30 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.